The Flavor and Fragrance High Production Volume Consortia

201-16676B

The Alicyclic Aldehyde Consortium

Revised Robust Summaries for HMPCC (2008)

3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde **CAS No. 31906-04-4**

FFHPVC Alicyclic Aldehyde Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:

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Robust Summaries for HMPCC

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al*., 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1.Reliable without restrictions
- Reliability code 2.Reliable with restrictions
- Reliability code 3.Not reliable
- Reliability code 4.Not assignable

1 CHEMICAL AND PHYSICAL PROPERTIES

1.1 Melting Point

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated/Adapted Joback Method
GLP	No
Melting Point	89.01 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) U S Environmental Protection Agency.

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated/Gold and Ogle Method
GLP	No
Melting Point	65.64 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) U S Environmental Protection Agency.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated/Mean of Joback and Gold and Ogle Methods
GLP	No
Melting Point	77.32 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) U S Environmental Protection Agency.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	EPIWIN
Input Parameters	Boiling point, 280 °C (exp); log Kow=2.1(exp) at 30 °C; vp=0.001 mm Hg at 25 °C (exp); water sol., 184.6 mg/L at 30°C
GLP	No
Melting Point	77.32 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References	Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637

1.2 Boiling Point

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Measured
GLP	No
Year	1985
Boiling Point	120 - 122 °C
Pressure	1.0 mm Hg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Bauer K. and Garbe D. (1985) Common Flavor and Fragrance Materials Verlagsgesellschaft mbH, D-6940, Weinheim, Federal Republic of Germany.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal
Method/guideline	Measured
GLP	No
Year	1987
Boiling Point	85 - 87 °C
Pressure	1.0 mm Hg

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Bauer K. and Garbe D. (1985) Common Flavor and Fragrance Materials Verlagsgesellschaft mbH, D-6940, Weinheim, Federal Republic of Germany.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated/Adapted Stein and Brown method
GLP	No
Boiling Point	307.07 °C
Pressure Unit	mm Hg
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) v1.40 U S Environmental Protection Agency.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated
Boiling Point	280 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal
Method/guideline	Calculated
Boiling Point	241 °C

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

1.3 Vapor Pressure

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated
GLP	No
Vapor Pressure	Less than 0.001 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated/Modified Grain method
GLP	No
Vapor Pressure	0.0000273 mm Hg
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) U S Environmental Protection Agency.

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal
Method/guideline	Determined from boiling point/pressure plot
GLP	No
Vapor Pressure	0.001 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standard boiling point-pressure plot.
References	Fragrance Materials Association (FMA) (1996) Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated/Modified Grain method
GLP	No
Vapor Pressure	0.0000274 mm Hg
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Data reported from chemical properties database.
References	Chemical Zoo (2007) Chemical Spiders DB.

1.4 n-Octanol/Water Partition Coefficients

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde

CAS No.	31906-04-4
Remarks for Substance	Purity: 22% 3-isomer, 75% 4-isomer by GC
Method/guideline	Reverse phase HPLC method (OECD 117)
Year	1996
Log Pow	2.1 at 25 °C
Remarks for Results	For both isomers
Data Qualities Reliabilities	Reliability code 3. Reliable without restrictions.
Remarks for Data Reliability	Code 3. Basic data obtained from OECD guideline/standard procedure.
References	Givaudan-Roure (1996) Partition coefficient n-octanol/water of HMPCC. Unpublished.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal
Method/guideline	Measured
GLP	Ambiguous
Year	1996
Log Pow	1.5
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Procter and Gamble Company (1996) Unpublished submission to EPA.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated
GLP	No
Log Pow	2.03
Data Qualities Reliabilities	Reliability code 4. Not assignable.

Remarks for Data Reliability	Code 4. Calculated.
References	Interactive Analysis LogP and LogW Predictor: Database contributed by Syracuse Research Corporation, SciVision, Albany Molecular Research, Inc., edu Soft LC, Cambridge Soft. www.logp.com.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal
Method/guideline	Calculated
GLP	No
Log Pow	2.11
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U S Environmental Protection Agency.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated
GLP	No
Log Pow	3.32
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

1.5 Water Solubility

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/Guideline	Calculated from Log Kow
GLP	No
Value (mg/L) at Temperature	184.6 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOW EPI Suite (2000) U S Environmental Protection Agency.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
GLP	No
Value (mg/L) at Temperature	1,045 mg/L
Remarks for Test Conditions	No temperature given.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Interactive Analysis LogP and LogW Predictor: Database contributed by Syracuse Research Corporation, SciVision, Albany Molecular Research, Inc., eduSoft LC, Cambridge Soft. www.logp.com.

2 ENVIRONMENTAL FATE AND PATHWAYS

2.1 Photodegradation

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated
Test Type	AOPWIN
Halflife t1/2	1.009 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

2.1 Stability in Water

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method	Calculated
Halflife t 1/2	1400 days at pH 8. Substance cannot be hydrolyzed.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	HYDROWIN EPI Suite (2000) US Environmental Protection Agency.

2.2 Biodegradation

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	>98% of 3-isomer and the 4-isomer
Method	OECD Guideline 301F
Test Type	Manometric Respirometry Test
GLP	Yes
Year	1996
Contact Time	28 days
Innoculum	Fresh activated sludge from a biological wastewater treatment plant treating predominantly domestic sewage was used.
Remarks for Test Conditions	The ready biodegradability of lyral was evaluated in a Manometric Respirometry Test. The sludge was collected in the morning, washed three times in the mineral medium (by centrifuging at 1000 g for 10 minutes, discarding the supernatant and resuspending in mineral medium) and kept aerobic until being used on the same day. The dry weight of suspended solids was determined by taking two 50 ml samples of the homogenized sludge, evaporating water on a steam bath, drying in an oven at 105-110 C for two hours and weighing the residue. The toxicity of the test chemical for the inoculum was checked. A pair of flasks of the volumetric respirometer (SAPROMAT D 12) were filled with: mineral medium + test chemical (100 mg/L) + aniline (100 mg/L) + inoculum, and their respirations were recorded as done for the other flasks. If they were lower than those of the flasks containing: mineral medium + aniline (100 mg/L) + inoculum, the test chemical can be assumed to be inhibitory to the inoculum used. Test material samples (25 mg, corresponding to 100 mg/l in a 250 ml flask) were weighed in small aluminum boats and added directly to the test flasks of the SAPROMAT, where as reference samples (aniline) were added as 1.0 ml of a 25 mg/ml solution in mineral medium. All flasks were partially filled with mineral medium. Samples of test or reference substance or both were added. Then, a volume of suspended sludge corresponding to 7.5 mg dry weight was added and the volume adjusted to 250 ml. The pH of each flask was measured and adjusted as necessary. About 2 g of soda lime was placed in an attachment of the stopper, then flasks closed and placed in the water bath of the SAPROMAT. After temperature and pressure equilibration, the oxygen meters of the instrument were set to zero (time zero of the experiment). Everyday the oxygen consumption of each flask was recorded and correct temperature and stirring were checked. At the end of the test period (normally 28 days), the pH of each flask was measured again. Nominal concentrations of test substance and reference substance (aniline) were 100 mg/L. Dry weight of suspended solids was 2.583 g/l. To obtain

	a concentration of 30 mg/l (dry weight) in a 250 ml flask, 2.90 ml of sludge was needed (inoculum). Test temperature was 22 C; test duration was 28 days.
Degradation % After Time	61.2% after 28 days
Remarks Results	The reference material was aniline and degradation of the substance exceeded 40% after 7 days and 65% after 14 days; thus the activity of the inoculum was verified and the test validated. % Biodegradation (nominal) of lyral after 28 days (95% confidence limits) = 62%.
Time required for 10% degradation	>10 days
10 day window criteria	The test material underwent 62% biodegradation after 28 days. Biodegradation started after a long (13-day) lag phase and reached 57% at the end of the 10-day window (days 13-23).
Total degradation	62% after 28 days
Classification	Under the conditions of this study, test material should be regarded as not readily biodegradable. However, the limits were close to the "pass" limit.
Conclusion Remarks	HMPCC was shown to be not readily biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Givaudan (1995) Ready biodegradability of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde. Unpublished report.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	22% of the 3-isomer and 76% of the 4-isomer
Method	OECD Guideline 301B
Test Type	Sealed vessel carbon dioxide production test
GLP	Yes
Year	1996
Contact Time	28 days
Innoculum	Secondary effluent from an unacclimatized activated sludge plant.
Remarks for Test Conditions	Test material was directly added to the incubation mixture. The incubation was 28 days. The nominal concentration was 10 mg/l organic carbon. The test temperature range was 17-22 °C. The test was conducted in 160 ml vessels (hypovials)

	containing 100 ml mineral salts medium inoculated with secondary effluent and the respective test or reference substance. The inoculum used was 10% by volume of activated sludge plant secondary effluent, filtered through a Whatman filter paper (541) to remove coarse particulate matter. The level of dissolved inorganic carbon (DIC) was reduced by sparging the filtered effluent with nitrogen after prior adjustment of the pH to 6.5. Test concentration was nominal 10 mg/l organic carbon. Test temperature range was 19-24 C. Multiple vessels were prepared per test material sealed with a butyl rubber septum and an aluminium crimp seal. The headspace in each vessel had a volume of 60 ml and when filled with air, contained approximately 6 times the mass of oxygen required for the complete oxidation of the test material. The sealed vessels were incubated at 20 C on a rotary shaker. At intervals during the 28 day test period a vessel was removed and concentration of carbon dioxide in the headspace gas determined. The seal is then broken and the concentration of inorganic carbon in the test medium was determined. Analysis of both the headspace gas and the liquid medium for CO2/DIC was performed on day numbers: 3, 7, 10, 14, 17, 21, 24 and 28 using the Ionics 555 Inorganic Carbon Analyser. The total inorganic carbon in the vessel was calculated and corrected by subtracting the inorganic carbon produced in the control. The control vessels were identical to the test vessels except for the omission of the test material.
Degradation % After Time	41.2% after 28 days
Remarks Results	% biodegradation (nominal) of test material after 28 days (95% confidence limits) = 41.2 (11.2-71.2).
Time required for 10% degradation	>10 days
10 day window criteria	No
Total degradation	No
Classification	The test material failed the test and therefore cannot be classified as readily and ultimately biodegradable
Conclusion Remarks	HMPCC was shown to be not readily and ultimately biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Quest International Ltd. (1996) The ultimate biodegradability of HMPCC in the sealed vessel test. Unpublished report.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method	"Standard Methods", authors did not provide detail

Test Type	Measured
GLP	Ambiguous
Year	1985
Remarks for Test Conditions	Test substance added by injection directly into BOD bottle due to limited solubility.
Degradation % After Time	Bio-oxidation (BOD/CODx100) = 10% on day 20
Results	Measured theoretical oxygen demand in mg O2/mg compound = 3.13
Time required for 10% degradation	20 days
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Waggy G.T. and Blessing, R.L. [1986] Ecological fate and effects testing of UCC products and wastewaters during 1985. UCC Business Confidential, Project Report dated March 11, 1986. Central Engineering Department, Union Carbide Corporation.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 4,4-dimethyl-3-cyclohexenecarboxaldehyde
Method	"Standard Methods", authors did not provide detail
Test Type	Measured
GLP	Ambiguous
Year	1985
Remarks for Test Conditions	Test substance added by injection directly into BOD bottle due to limited solubility
Degradation % After Time	Biooxidation (BOD/CODx100) = 10% on day 20
Results	Measured theoretical oxygen demand in mg O2/mg compound = 2.75
Time required for 10% degradation	20 days
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Waggy G.T. and Blessing R.L. [1986] Ecological fate and effects testing of UCC products and wastewaters during 1985.

	UCC Business Confidential, Project Report dated March 11, 1986. Central Engineering Department, Union Carbide Corporation.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal
Method	Method F from the Blue Book Series, Assessment of Biodegradability 1981
Test Type	Measured
GLP	No
Year	1990
Contact time (units)	28 days
Innoculum	Activated sludge from sewage
Remarks for Test Conditions	The test material was diluted to 52.5 mg DOC/L in buffered solution containing 30 mg activated sludge solids/L. The mixture was agitated at 20 °C over 28 days with periodic measurements of dissolved organic carbon.
Degradation % After Time	As % removal of DOC: day 0, 1, 2, 5, 7, 9, 12, 15, and 19 was 0, 6.2, 0.8, 46, 84.1, 90.5, 91.9, 97.9, and 99.8, respectively.
Results	A better than 95% COC removal was achieved within 19 days and therefore the study was terminated.
Time required for 10% degradation	Less than 5 days
10 day window criteria	Yes
Total degradation	99.8% at 19 days
Conclusion Remarks	Hydroxycitronellal has a high degree of biodegradability.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Stickley D.P. (1990) Report to Bush Boake Allen Limited on Biodegradability of Citral 900UC and Hydroxy Citronellal Pure 55. Berridge Environmental Laboratories Limited. Report No. 8347 dated February 15, 1990.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4

Remarks for Substance	Data is for structurally related substance 7-hydroxycitronellal (purity 95.0%)
Method	Sealed vessel test (OECD Guideline 301B)
Test Type	CO2 production test
GLP	Ambiguous
Year	1990
Contact time (units)	28 days
Innoculum	Secondary effluent from an unacclimatized activated sludge plant
Remarks for Test Conditions	The test concentration was nominal 10 mg/L organic carbon with a test temperature range of 20 to 24 °C. Sealed vessels were incubated on a rotary shaker.
Degradation % After Time	For day 4, 7, 11, 14, 18, 21, 25, and 28 was 3.8, 64.7, 66.3, 78.3, 80.5, 90.5, 85.5, and 93.7, respectively.
Results	95% confidence interval of 87.9 to 99.5
Time required for 10% degradation	5 days
Classification	Readily and ultimately biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	King J.M.H. (1994) The Biodegradability of Perfume Ingredients. Unilever Research.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method	Linear model prediction; non-linear model prediction; MITI linear model prediction; MITI non-linear model prediction
Test Type	Calculated
GLP	No
Results	Biodegrades fast.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	BIOWIN EPI Suite (2000) U S Environmental Protection Agency.

2.3 Fugacity

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Remarks for Test Conditions	VP=0.0000274 mm Hg, log Kow=2.1, MP= -77 ^{o}C, BP= 280 ^{o}C water solubility=184.6 mg/L, Henry's LC
Year	2000
Media	Air-Water-Soil-Sediment Partition Coefficients
Model data and results	Compartment half-lives, hours: Air=0.486; Water=900;Soil=900;Sediment=3600
Estimated Distribution and Media Concentration	Air=0.043% Water=38.7% Soil=61.1% Sediment=0.155%
Conclusion remarks	Substance is predicted to persist in the environment for 564 hours.
Model data and results	Reliability code 4. Not assignable.
Data Qualities Reliabilities	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
Remarks for Data Reliability	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Model Conditions	25 C, 100,000 lbs

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Remarks for Test Conditions	The input parameters used were molecular weight, melting point (77.32 °C) and boiling point (307.07 °C).
Input Parameters	MW, calculated VP, calculated MP
Media	Air
Estimated Distribution and Media Concentration	0.0153%
Model data and results	half life = 0.486 hrs for 1000 kg/hr emission rate
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. *Environmental Toxicology and Chemistry*, **15(9),** 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. *Environmental Toxicology and Chemistry*, **15(9),** 1627-1637.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Model Conditions	25 C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Remarks for Test Conditions	The input parameters used were molecular weight, melting point (77.32 °C) and boiling point (307.07 °C).
Input Parameters	MW, calculated VP, calculated MP
Media	Water
Estimated Distribution and Media Concentration	25.5%
Model data and results	half life=900 hrs for 1000 kg/hr emission rate

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. *Environmental Toxicology and Chemistry*, **15(9),** 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. *Environmental Toxicology and Chemistry*, **15(9),** 1627-1637.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Model Conditions	25 C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Remarks for Test Conditions	The input parameters used were molecular weight, melting point (77.32 °C) and boiling point (307.07 °C).
Input Parameters	MW, calculated VP, calculated MP
Media	Soil
Estimated Distribution and Media Concentration	74.5%
Model data and results	half life = 900 hrs for 1000 kg/hr emission rate
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. *Environmental Toxicology and Chemistry*, **15(9),** 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. *Environmental Toxicology and Chemistry*, **15(9),** 1627-1637.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde

CAS No.	31906-04-4
Model Conditions	25 C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Remarks for Test Conditions	The input parameters used were molecular weight, melting point (77.32 °C) and boiling point (307.07 °C).
Input Parameters	MW, calculated VP, calculated MP
Media	Sediment
Estimated Distribution and Media Concentration	0.81%
Model data and results	half life= 3600 hrs for 0 kg/hr emission rate
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. *Environmental Toxicology and Chemistry*, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

3 ECOTOXICITY

3.1 Acute Toxicity to Fish

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substances	22% of the 3-isomer and 76% of the 4-isomer
Method/guideline	96-Hour semi-static toxicity test
Test Type	Experimental
Species/Strain/Supplier	Fathead minnow/Pimephales promelas/Aquatic Biosystems, Inc.
GLP	Yes (OECD Guidelines 203, 1992)
Year	2003
Remarks for Test Conditions	Juvenile fathead minnows (72 hours old) were maintained at the contract laboratory under static renewal conditions for 72hours. Prior to testing the temperature and dissolved oxygen were 22.0-22.8C and 7.2-9.0 mg/L, respectively. For three days before the test were fed live Artemia salina nauplii. Fish were not fed during testing. Range-finding tests were performed under static conditions in sealed vessels. Survival was 100% at 0, 0.1, 1.0, and 10 mg/L but 0% at 100 mg/L. The definitive 96-hour test was performed under semi-static conditions with 24 hour renewal. Groups of ten fish were added to 6 nominal concentrations of HMPCC. A concurrent control group was also evaluated. Test solutions were maintained under 16 hours of light and 8 hours of darkness. At 24, 48, 72, and 96 hours, the number of surviving fish and sublethal observations were recorded. Test vials remained sealed during the experiment. Dissolved oxygen, pH, conductivity, and temperature were measured at 24-hour intervals. Concentrations of the test material were measured by HPLC at 0, 24 hours prior to renewal and at 24 hour intervals up to 96 hours. Standard 48, 72, and 96 hour LC50 values were calculated using probit method (Stephan, 1978). NOEC values were also noted.
Conclusion Remarks	Exposure of fathead minnows, *Pimephales promelas,* to HMPCC resulted in a 96 hour median lethal concentration (LC50) of 11.8 mg/L (95% confidence interval = 10.2 to 13.6 mg/L). The 96 hour no observed effect concentration (NOEC) is 8.21 mg/L.
Remarks for Results	The cumulative number of live organism in duplicate tests at each 24-hour interval and the corresponding concentrations in mg HMPCC/L at t=0, t=24, 48, 72, and 96 hours were measured. Mean measured concentrations of HMPCC were: ND (none detected at or above the limit of quantitation; control),

	8.21, 15.1, 24.3, 42.5, and 73.0 mg/L (Table 2). Measured concentrations in samples collected after 48 and 96 hours were 84 to 97% of the initial measured concentrations, indicating that once the aqueous solutions of lyral were sealed into the test vessels with the fathead minnows, concentrations remained constant. Mean measured concentrations ranged from 82 to 91% of nominal concentrations.
Analytical monitoring	GC
Unit	mg/L
Exposure period (unit)	96 hrs
Nominal concentrations as mg/L	0 mg/L (control), 10, 18, 29, 48, and 80
Measured concentrations as mg/L	0, 8.21, 15.1, 24.3, 42.5, and 73.0 mg/L
Endpoint value	96-hr LC50 = 11.8 mg/L
Remarks fields for results	Exposure of fathead minnows, *Pimephales promelas,* to lyral resulted in a 96 hour median lethal concentration (LC50) of 11.8 mg/L (95% confidence interval = 10.2 to 13.6 mg/L). The 96 hour no observed effect concentration (NOEC) is 8.21 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. OECD 203 Guideline study.
References	Ward T (2003) Acute toxicity test with Lyral. and the fathead minnow (Pimephales promelas). Study Number 2506-FF. Private Communication to FFHPVC. Unpublished report.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 3-cyclohexene-1-carboxaldehyde
Method/guideline	Acute lethal toxicity (14-day LC50) - semi static
Test Type	Experimental
GLP	No
Year	1988
Species/Strain/Supplier	Guppy (*Poecilia reticulata*)
Exposure Period	14 days
Analytical monitoring	GC Analysis

Remarks for Test Conditions	Over 14 days, groups of 10 guppies (2-3 months old) were exposed to five concentrations of test substance in 1.5 L glass vessels containing 1.41 L test solution which was renewed daily. Control fish were exposed to 72 ul acetone/L. O2 content, pH and test substance concentration were determined before and after test solution renewal. LC50s were determined using logit transformation and corrected for loss of test substance.
Unit	umol/L
Endpoint value	LC50 = 10.2 (21.4 mg/L)
Remarks fields for results	LC50 reported at log 1.01. The LC50 was not corrected for loss of test substance because no reliable recovery factors could be determined. The authors attributed this to irreproducible results during analysis of the aqueous solution. pH values ranged from 6.5-7.5. O2 content was often low (3 mg/L) 24 hours following preparation of test solutions. The authors attributed this to bacterial growth and disregarded data from tests with low O2 content accompanied by mortality.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Deneer J.W., Seinen, W., Hermens, J.L.M. (1988) The acute toxicity of aldehydes to the guppy. Aquatic Toxicol 12:185-192.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	ECOSAR
Test Type	Calculated
GLP	No
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Remarks for Test Conditions	Based on: log KOW = 3.32, MP = 77.32 °C, water solubility = 49.71 mg/L
Unit	mg/L
Endpoint value	LC50 = 6.787
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	ECOSAR
Test Type	Calculated
GLP	No
Species/Strain/Supplier	Fish
Exposure Period	14 days
Remarks for Test Conditions	Based on: log KOW = 3.32, MP = 77.32 °C, water solubility = 49.71 mg/L
Unit	mg/L
Endpoint value	LC50 = 20.006
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	EPA Committee on Methods for Toxicity Tests with Aquatic Organisms
Test Type	Experimental
GLP	Ambiguous
Year	1985
Analytical procedures	Not stated
Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
Remarks for Test Conditions	Groups of 10 very young (less than 2 days) *Daphnia magna* were exposed to 5-10 concentrations of test substance or control in 250 ml beakers containing 200 ml test solution over a period of 48 hours. Dissolved oxygen and pH were determined at the beginning of the test and after 48 hours. Mortalities were recorded at 24 and 48 hours. Kanawha River water was used in the test and analyses were conducted: total hardness = 55 mg/L as CaCO3 total alkalinity = 36 mg/L as CaCO3 pH= 6.7 conductivity = 250 umhos/cm
EC50, EL50, LC0, at 24,48 hours	48-hour LC50 = 76 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Waggy G.T., Blessing, R.L. (1986) Ecological fate and effects testing of UCC products and wastewaters during 1985. UCC Business Confidential, Project Report dated March 11, 1986. Central Engineering Department, Union Carbide Corporation.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4

Remarks for Substance	Data is for structurally related substance 4,4-dimethyl-3-cyclohexenecarboxaldehyde
Method/guideline	EPA Committee on Methods for Toxicity Tests with Aquatic Organisms
Test Type	Experimental
GLP	Ambiguous
Year	1985
Analytical procedures	Not stated
Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
Remarks for Test Conditions	Groups of 10 very young (less than 2 days) *Daphnia magna* were exposed to 5-10 concentrations of test substance or control in 250 ml beakers containing 200 ml test solution over a period of 48 hours. Dissolved oxygen and pH were determined at the beginning of the test and after 48 hours. Mortalities were recorded at 24 and 48 hours. Kanawha River water was used in the test and analyses were conducted: total hardness = 55 mg/L as CaCO3 total alkalinity = 36 mg/L as CaCO3 pH = 6.7 conductivity = 250 umhos/cm
EC50, EL50, LC0, at 24,48 hours	48-hour LC50 = 76 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Waggy G.T., Blessing, R.L. (1986) Ecological fate and effects testing of UCC products and wastewaters during 1985. UCC Business Confidential, Project Report dated March 11, 1986. Central Engineering Department, Union Carbide Corporation.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Calculated
Test Type	ECOSAR
Species/Strain/Supplier	Daphnia magna
Test Details	48 hours
EC50, EL50, LC0, at 24,48	LC50 = 1.733 mg/L

hours	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U S Environmental Protection Agency.

3.3 Acute Toxicity to Aquatic Plants

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substances	22% of the 3-isomer and 76% of the 4-isomer
Method/guideline	OECD 201 Guideline
Test Type	Experimental
GLP	Yes
Year	2003
Species/Strain/Supplier	Green algae/Selenastrum capricornutum/UTEX 1648
Exposure period (duration)	72 hrs
Analytical monitoring	HPLC/UV detector
Remarks for Test Conditions	Green Algae/Selenastrum capricornutum/U. of Texas was maintained at test conditions for 14 days prior to the test. The culture was growing in at least 2 subcultures prior to the initiation of the test. At the conclusion of the test, the number of cells/mL in the 10 mg/L test vessels was 128% of the number of cells/mL in the control flask and the number of cells/mL in the 100 mg/L test vessels was 2% of the number of cells/mL in the control flask after three days. In the definitive test, algae was treated with nominal concentrations of 0, 6.5, 13, 25, 50, and 100 mg/L for 72 hours. pH was adjusted to 7.5 and solutions were exposed for 24 hours of light of intensity, 400-410 foot candles. The number of algal cells/mL as well as relative size, cell shapes, color, adherence and aggregation of cells was determined. Water quality measurements were made and each solution was inoculated with approximately 10,000 algal cells/mL. At 24, 48, and 72 hours 3 treatment and 6 control vessels were sacrificed to determine the number of algal cells/mL. Concentrations were determined by HPLC.

Nominal concentrations as mg/L	Nominal concentrations of lyral were 0 mg/L (control), 6.5, 13, 25, 50, and 100 mg/L.
Measured concentrations as mg/L	Initial measured concentrations of lyral were: ND (none detected at or above the limit of quantitation; control), 5.95, 11.9, 22.9, 45.7, and 98.4 mg/L. These initial measured concentrations, which ranged from 91 to 98% of the nominal concentrations, were used to calculate median effective concentrations (EC50s). Final measured concentrations were ND, 2.00, 4.17, 11.0, 32.5, and 74.4 mg/L.
Unit	mg/L
NOEC, LOEC or NOEL, LOEL	Exposure of algae to lyral for 72 hours resulted in a median effective concentration (EC50) of 25.4 mg/L when calculated using the average specific growth rate, 13.7 mg/L when calculated using the number of cells/mL, and 13.8 mg/L when calculated using the area under the growth curve. The 72 hour no observed effect concentration (NOEC) is 5.95 mg/L lyral when determined using the number of cells/mL, the average specific growth rate, and the area under the growth curve.
Biological observations	At the conclusion of the definitive toxicity test, a 0.5mL aliquot of test media from each test vessel where growth was maximally inhibited (22.9, 45.7, and 98.4 mg/L lyral concentrations) was combined with 100 mL of fresh media in a 250-mL flask. The cultures were incubated under test conditions for up to 168 hours. During this period the number of algal cells increased from an initial calculated concentration of 700, 350, and <150 cells/mL, respectively, to approximately 155,000, 77,000, and 1,330,000 cells/mL, indicating that the toxic effects were algistatic rather than algicidal.
Appropriate statistical evaluations?	EC50 values determined by weighted least squares non-linear regression (Bruce and Versteeg, 1992); NOEC was determined using a one-way analysis of variance (ANOVA) and Bonferroni's test (Gulley et al. 1990)
Conclusion remarks	The acute toxicity of lyral measured as a 50% decrease in growth and reproduction of freshwater algae was estimated to be 72 hr EC50=25.4 mg/L based on average specifc growth rate; 72-hr EC50=13.7mg/L calculated using the number of cells/mL; 72-hr EC50=13.8 mg/L using the area under the growth curve. The 72-hr NOEC=5.95 mg/L
Reliabilities	Relabitiy code 1. Reliable without restrictions.
Remarks for Data Reliability	OECD 201 Guideline study
References	Boeri R.L. (2003) The growth and reproduction toxicity test with lyral and freshwater alga, Selenastrum capricornutum. OECD 201. Study No. 2505-FF. Private Communication to FFHPVC. Unpublished Report.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4

Method/guideline	ECOSAR
Test Type	Calculated
GLP	No
Species/Strain/Supplier	Green algae
Exposure Period	96 hours
Remarks for Test Conditions	Based on: log KOW = 3.32, MP = 77.32 °C, water solubility = 49.71 mg/L
Endpoint Value	EC50 = 7.091 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

4 HUMAN HEALTH TOXICITY

4.1 Acute Toxicity

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Test Type	Acute oral toxicity
GLP	No
Year	1977
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Oral
Remarks for Test Conditions	Rats were orally administered HMPCC, 5000 mg /kg bw and observed for 14 days.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg bw
Number of deaths at each dose level	2 deaths on day 1
Remarks for Results	Rats exhibited slight lethargy, tremors, flaccid tone and piloerection. At necropsy, 2 rats were reported to have dark livers, 2 rats had light yellow intestines and 1 rat had dark kidney.
Conclusion remarks	The oral LD50 of HMPCC in rats was reported to be greater than 5000 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Opdyke D.L. (1977) Acute Oral Toxicity in Rats. Dermal Toxicity in Rabbits, Lyral. Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4

Test Type	Acute oral toxicity
GLP	Yes
Year	1982
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Groups of 5 rats/sex were administered a single dose of HMPCC, 4.0, 4.5, 5.0, 5.5 or 6.0 ml/kg bw by gavage and observed for 14 days.
Value LD50 or LC50 with confidence limits	Greater than 5,000 ml/kg bw
Number of deaths at each dose level	4.0 ml/kg bw: 2/5 males, 1/5 females 4.5 ml/kg bw: 0/5 males, 3/5 females 5.0 ml/kg bw: 1/5 males, 3/5 females 5.5 ml/kg bw: 1/5 males, 3/5 females 6.0 ml/kg bw: 2/5 males, 3/5 females
Remarks for Results	Necropsy findings of rats dying on the study included distended fluid-filled intestines and bladder, bright red lungs and blanched adrenals. Necropsy of surviving animals showed no remarkable findings.
Conclusion remarks	HMPCC shows a low order of acute oral toxicity in rats with an LD50 greater than 5000 ml/kg bw.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Mallory V.T., Naismith, R.W., Matthews, R.J. (1982) Acute oral toxicity study in rats (14 day). PH 402-IFF-005-81. 81-218-01. Pharmakon Research International Inc., Waverly, PA.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data is for structurally related substance 7-hydroxycitronellal
Test Type	Acute oral toxicity
GLP	No
Year	1973

Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Oral
Remarks for Test Conditions	Rats were orally administered 7-hydroxycitronellal, 5000 mg/kg and observed for 14 days.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg
Number of deaths at each dose level	1/10 on day 7 1/10 on day 11
Remarks for Results	No symptomatology reported.
Conclusion remarks	The oral LD50 of 7-hydroxycitronellal in rats was reported to be greater than 5,000 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Opdyke D.L. (1973) Acute oral toxicity in rats. Dermal toxicity in rabbits. Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Purity greater than 88%; 0.02% acrolein; less than 10% myrac, less than 2.5% myrcenol; mol wt = 210.3
Test Type	Acute oral LD50
GLP	No
Year	1987
Species/strain	Rat
Sex	Male and Female
# of animals per sex per dose	5
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Groups of male and female rats were administered a single dose of HMPCC, 2.0, 4.0, 8.0 or 16.0 ml/kg bw by perioral intubation and observed for 14 days. Five female rats also received 1.0 ml/kg bw of HMPCC.
Value LD50 or LC50 with	LD50 for males = 7.46 ml/kg bw (95% CL = 5.16-10.8)

confidence limits	LD50 for females = 3.25 ml/kg bw (95% CL = 2.02-5.24)
Number of deaths at each dose level	Deaths occurred between 4 hours and 3 days following treatment. 1.0 ml/kg bw - 0/5 females 2.0 ml/kg bw - 0/5 males; 1/5 females 4.0 ml/kg bw - 0/5 males; 3/5 females 8.0 ml/kg bw - 3/5 males; 5/5 females 16 ml/kg bw - 5/5 males; 2/2 females
Remarks for Results	Signs exhibited included sluggishness, lacrimation, tremors, kyphosis, red discharge around mouth, nose and eyes, unkempt appearance and prostration. Necropsy of affected rats showed pink or red lungs, distended and gas-filled stomachs and some gas-filled intestines. Survivors showed recovery within 1-5 days and had no remarkable lesions.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Myers R.C., Slesinski R.S., Frank F.R. (1987) Lyral (crude) [4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde]. Acute Toxicity and Primary Irritancy Studies. Bushy Run Research Center, Export, PA. Report No. 49-180 dated February 6, 1987.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Test Type	Acute dermal toxicity
GLP	No
Year	1977
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Dermal
Remarks for Test Conditions	Rabbits were dermally treated with HMPCC, 5000 mg/kg bw and observed for 14 days.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg bw
Number of deaths at each	1 death on day 7

dose level	1 death on day 13
Remarks for Results	The rabbit that died on day 7 appeared emaciated, lethargic and ptotic with discharge from nose and eyes 1 day prior to death. At necropsy, this animal had dried fecal material in anogenital region, exudate in the nose and mouth, small spleen, mottled kidney and redness in portions of the colon. At necropsy of the other animals, 1 rabbit had blotchy liver, 2 had mottled kidneys, and 1 had yellowish nodules on the liver. With respect to skin irritation, redness was slight in 5 rabbits, moderate in 4 rabbits and severe in 1 rabbit. Edema was slight in 2 rabbits and moderate in 8 rabbits.
Conclusion remarks	The dermal LD50 of HMPCC in rabbits was reported to be greater than 5,000 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Opdyke D.L. (1977) Acute Oral Toxicity in Rats. Dermal Toxicity in Rabbits, Lyral. Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Purity greater than 88%; 0.02% acrolein; less than 10% myrac, less than 2.5% myrcenol; mol wt = 210.3
Test Type	Acute dermal LD50
GLP	No
Year	1987
Species/strain	Rabbit
Sex	Male and Female
# of animals per sex per dose	5
Route of Administration	Dermal
Remarks for Test Conditions	Groups of male and female rabbits were administered a single dose of HMPCC, 4.0, 8.0 or 16.0 ml/kg bw by dermal application and observed for 14 days.
Value LD50 or LC50 with confidence limits	LD50 for males = 11.3 ml/kg bw (95% CL = 4.5-28.5) LD50 for females = 13.5 ml/kg bw (95% CL = 5.4-33.6)
Number of deaths at each dose level	Deaths occurred between 1 and 3 days following treatment. 4.0 ml/kg bw - 0/5 males; 0/5 females 8.0 ml/kg bw - 2/5 males; 1/5 females

	16 ml/kg bw - 3/5 males; 3/5 females
Remarks for Results	Signs exhibited included sluggishness, unsteady gait, nasal discharge, salivation and prostration. Dermal effect included erythema, edema, ecchymosis, necrosis, fissuring, crusty texture, desquamation, scabs, alopecia and ulceration. Gross pathology showed subcutaneous edema, mottled and red lungs and tracheas with red patches. Survivors showed recovery within 7-14 days.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Myers R.C., Slesinski R.S., Frank F.R. (1987) Lyral (crude) [4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde]. Acute Toxicity and Primary Irritancy Studies. Bushy Run Research Center, Export, PA. Report No. 49-180 dated February 6, 1987.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data is for structurally related substance 7-hydroxycitronellal
Test Type	Acute dermal toxicity
GLP	No
Year	1973
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	2
Route of Administration	Dermal
Remarks for Test Conditions	Rabbits were topically administered 2000 mg/kg of 7-hydroxycitronellal and observed for 14 days.
Value LD50 or LC50 with confidence limits	Greater than 2000 mg/kg.
Number of deaths at each dose level	No deaths.
Remarks for Results	No symptomatology reported; however there was insufficient material for a complete determination.
Conclusion remarks	The dermal LD50 of 7-hydroxycitronellal in rabbits was reported to be greater than 2,000 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Opdyke D.L. (1973) Acute oral toxicity in rats. Dermal toxicity in rabbits. Unpublished report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data is for structurally related substance 4,4-dimethyl-3-cyclohexenecarboxaldehyde
Test Type	Acute vapor inhalation toxicity test
GLP	No
Year	1986
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5
Route of Administration	Inhalation
Remarks for Test Conditions	Groups of rats (5/sex) were exposed in a dynamic system to 459, 521, or 558 ppm 4,4-dimethyl-3-cyclohexenecarboxal vapor for 4 hours and observed for 14 days. Similarly groups of rats (5/sex) were exposed to 365 or 402 ppm 4,4-dimethyl-3-cyclohexenecarboxaldehyde vapor for 1 hour in a static system and observed for 14 days. In the dynamic system, compressed air was passed through a bottle containing crude 4,4-dimethyl-3-cyclohexenecarboxaldehyde and the vapor entered the inhalation chamber either undiluted or diluted to the target concentration with filtered air. For the 521 ppm exposure group, a fresh test sample was introduced after 2 hours. For the static exposure groups, the test substance was left in a sealed 120 L chamber for 18-19 hours prior to introducing the rats. For the 365 ppm exposure, the test material was sparged with N2 gas for 2 hours prior to enclosing in the chamber.
Number of deaths at each dose level	Deaths occurred on days 1 or 2 post-exposure. Dynamic system: 521 ppm: 1/5 males; 3/5 females 459 and 558 ppm: 0/5 males; 0/5 females Static system: 365 and 402 ppm: 0/5 males; 0/5 females
Remarks for Results	Dynamic system At 558 ppm, acrolein vapor of 42 ppm was detected. After 20 min, no acrolein vapor was detected (DL = 10 ppm). Signs exhibited included lacrimation, perioral wetness and respiratory

	difficulties on day of exposure. No clinical signs or macroscopic lesions were reported post exposure. Static system For 365 and 402 ppm, acrolein vapor was 2.0 and 8.4 ppm, respectively. Signs exhibited included lacrimation and periocular wetness. No clinical signs or macroscopic lesions were reported post exposure.
Conclusion remarks	The authors considered the deaths reported at 558 ppm to be related to the initial acrolein exposure of 42 ppm since the 1-hour rat LC5 of acrolein is 26 ppm. Therefore, no mortalities were attributed to 4,4-dimethyl-3-cyclohexenecarboxaldehyde exposure.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Union Carbide (1987) Aldehyde AA (crude). Acute vapor inhalation toxicity test. Bushy Run Research Center. Project No. 50-54 dated April 27, 1987.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Purity greater than 88%; 0.02% acrolein; less than 10% myrac, less than 2.5% myrcenol; mol wt = 210.3
Test Type	Static 6-hour inhalation toxicity test
GLP	No
Year	1987
Species/strain	Rat
Sex	Male and Female
# of animals per sex per dose	5
Route of Administration	Inhalation
Remarks for Test Conditions	Groups of male and female rats were exposed to a statically generated substantially saturated HMPCC vapor for 6 hours and observed for 14 days.
Number of deaths at each dose level	No deaths occurred.
Remarks for Results	No signs of toxicity and no remarkable gross pathology.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.

References	Myers R.C., Slesinski R.S., Frank F.R. (1987) Lyral (crude) [4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde]. Acute Toxicity and Primary Irritancy Studies. Bushy Run Research Center, Export, PA. Report No. 49-180 dated February 6, 1987.

4.2 Genetic Toxicity

4.2.1 *In vitro* Genotoxicity

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Assay:> 96%
Method/guideline	Two phase reverse mutation assay
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	Yes
Year	2001
Species/Strain	Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537
Metabolic Activation	S9 from Aroclor 1254-induced rat liver
Doses/Concentration	Six concentration in the range from 75 to 5000 ug/plate
Remarks for Test Conditions	A two-phase bacterial reverse mutation assay was conducted with the test materials in DMSO using Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537 with and without Aroclor-induced rat liver S9. The preliminary toxicity assay was the first phase of the study and was used to establish a dose-range over which the test article would be assayed. The mutagenicity assay was the second phase and was used to evaluate the mutagenic potential of the test compounds. The positive control for assays with S9 was 1.0 ug/plate 2-aminoanthracene, and for assays without S9 was 1.0 ug/plate 2-nitrofluorene (strain TA98), 1.0 ug/plate sodium azide (strains TA100 and TA1535) or 75 ug/plate 9-aminoacridine (strain TA1537). For test materials to be considered positive they must cause a dose-related increase in the mean revertants/plate of at least one tester strain with a minimum of two increasing concentrations of the test material.
Results	No significant increase in the numbers of revertant colonies was recorded for any of the bacterial strains with any dose of lyral

	either with or without metabolic activation.
Cytotoxic concentration	5000 ug/plate
Genotoxic Effects	None
Conclusion Remarks	Lyral was found to be non-mutagenic under the conditions of this test.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Cocchiara, J. A.M.Api and D.Jacobson-Kram. (2001) In vitro and in vivo evaluation of the genotoxic potential of three aldehydes used as fragrance ingredients. *The Toxicologist*, 60(1), 101-102.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Assay:> 96%
Method/guideline	Plate incorporation method
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	Yes
Year	1999
Species/Strain	Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538
Metabolic Activation	S9 from Aroclor 1254-induced rat liver
Doses/Concentration	Six concentration in the range from 10 to 5000 ug/plate
Remarks for Test Conditions	S. typhimurium strains TA1535, TA1537, TA98, TA100, TA1538 and E coli strains WP2uvrA were treated with lyral by the preincubation method at six dose levels, in duplicate, both with and without the addition of a rat liver homogenate metabolising system (S9Mix). In this case the dose range of lyral was 10 to 5000 ug/plate. The solvent (dimethyl sulphoxide) control plates gave counts of revertant colonies within the normal range. All positive control chemicals gave increases in revertants, both with and without the metabolising system, within expected ranges. Lyral caused a reduction in the growth of the bacterial lawn at dose of 5000 ug/plate in any strain of S. typhimurium and E. coli.
Results	No significant increase in the numbers of revertant colonies was recorded for any of the bacterial strains with any dose of lyral

	either with or without metabolic activation.
Cytotoxic concentration	5000 ug/plate
Genotoxic Effects	None
Conclusion Remarks	Lyral was found to be non-mutagenic under the conditions of this test.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Takasago International Corporation [1999] 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde: Reverse mutation test "Ames test" with S. typhimurium and E. coli. Private communication to RIFM. Unpublished Report.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data is for structurally related substance 2,4-dimethyl-3-cyclohexene-1-carboxaldehyde
Method/guideline	Plate incorporation method
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	Yes
Year	1995
Species/Strain	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538
Metabolic Activation	S9 from Aroclor 1254-induced rat liver
Doses/Concentration	0.03, 0.10, 0.30, 1.0, and 3.0 mg/plate
Remarks for Test Conditions	A preliminary cytotoxicity assay was conducted to determine appropriate concentrations for the mutagenicity study. 2,4-Dimethyl-3-cyclohexene-1-carboxaldehyde was tested at concentrations of 0.03, 0.10, 0.30, 1.0, or 3.0 mg/plate. Acetone was the solvent used. The positive controls used were 4-nitro-o-phenylenediamine, sodium azide, 2-aminoanthracene, and 9-aminoacridine. Treated cultures (in triplicate) were incubated in the presence or absence of S9 at 37 deg C for 48-72 hours. Colonies were counted either manually or with an Artek Model No. 880 Colony Counter. The test substance was considered positive for mutagenicity if it "consistently produced a dose-related increase in the mean reversion frequency of at least one bacterial strain as compared to the vehicle control for that strain. At least one of those doses must have produced a mean reversion frequency at least twice that of the vehicle control."

	The test substance was also considered a bacterial mutagen if a "reproducible increase in the mean number of revertant colonies at a single dose level of at least 2-fold compared to the vehicle control" was noted.
Results	Mean plate counts without S9 for solvent control, 0.03, 0.10, 0.30, 1.0 and 3.0 mg/plate: TA98: 24, 22, 22, 23, 19, and toxic TA100: 98, 89, 99, 91, 86, and toxic TA1535: 7, 10, 9, 9, 4, and toxic TA1537: 7, 6, 6, 5, 5, and toxic TA1538: 11, 13, 14, 16, 14, and toxic Mean plate counts with S9 for solvent control, 0.03, 0.10, 0.30, 1.0 and 3.0 mg/plate: TA98: 34, 23, 27, 31, 27, and 17 TA100: 106, 99, 114, 112, 96, and 82 TA1535: 11, 11, 9, 8, 9, and 8 TA1537: 6, 5, 6, 3, 6, and 3 TA1538: 20, 19, 15, 17, 3 (toxic), and 10 Similar results were reported in a repeat experiment. All 5 strains showed appropriate responses to the positive controls.
Cytotoxic concentration	1.0 mg/plate
Genotoxic Effects	None
Conclusion Remarks	2,4-Dimethyl-3-cyclohexene-1-carboxaldehyde was not a bacterial mutagen in this assay.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Vergnes J.S., Morabit, E.R. [1995] Aldehyde AA (Crude): Mutagenic Potential in the Salmonella/Microsome (Ames) Assay. 2,4-Dimethyl-3-cyclohexene-1-carboxaldehyde. Bushy Run Research Center. No. 94U1472. March 3, 1995.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Plate incorporation method (Maron and Ames, 1983)
Test Type	Ames reverse mutation

System of Testing	Bacterial
GLP	Yes
Year	1999
Species/Strain	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537; *Escherichia coli* strain WP2 uvrA
Metabolic Activation	S9 from Aroclor 1254-induced rat liver
Doses/Concentration	Vehicle, 75, 200, 600, 1,800, and 5,000 ug/plate
Remarks for Test Conditions	Dimethyl sulfoxide was used as the test vehicle. A preliminary toxicity assay was conducted using concentrations up to 5,000 ug/plate to determine appropriate test concentrations. Lyral was tested both in the presence and absence of S9. Plates were plated in triplicate and incubated for 48 to 72 hours at 37 deg C. Any plates not counted immediately were stored at 2-8 deg C. Colony counting was conducted either entirely by automated colony counter or entirely manually. Any plates with sufficient precipitate to interfere with the automatic counter were counted manually. Positive controls used were 2-aminoanthracene, 2-nitrofluorene, sodium azide, 9-aminoacridine and methyl methansulfonate. To be considered a positive finding, the increase in mean revertants at the peak of the dose response must have been equal to 3 times (for TA1535 and TA1537) or 2 times (for TA98, TA100 and WP2 uvrA) the mean vehicle control value. The test substance was considered positive if it caused a dose-related increase in the mean revertants/plate of at least one tester strain with a minimum of 2 increasing concentrations.
Results	No precipitate was observed. Toxicity was reported in strains TA98 and TA1537 at 5,000 ug/plate. No positive responses were reported; however, a non-dose-related increase was reported in TA98 (1.8-fold increase) and TA100 (1.5-fold increase) in the absence of S9. Lyral was retested in TA98 and TA100 without S9 resulting in a non-dose-related increase in TA98 (2.4-fold) and no effect in TA100. The average revertants/plate in the absence of S9 are as follows for vehicle, 75, 200, 600, 1,800, 5,000 ug/plate and positive control, respectively: TA98: 14, 10, 16, 21, 25, 10 and 486 TA100: 135, 148, 159, 174, 169, 202, and 582 TA1535: 7, 7, 8, 7, 11, 9, and 459 TA1537: 8, 10, 8, 10, 10, 3, and 617 WP2 uvrA: 17, 19, 17, 12, 13, 13, and 173 The average revertants/plate in the presence of S9 are as follows for vehicle, 75, 200, 600, 1,800, 5,000 ug/plate and positive control, respectively: TA98:20, 22, 20, 22, 27, 25, and 851

	TA100: 173, 180, 190, 177, 177, 203, and 706 TA1535: 9, 9, 12, 13, 13, 8, and 72 TA1537: 10, 11, 9, 12, 11, 9, and 71 The average number of revertants/plate in the repeat assay for strains TA98 and TA100 without S9 were as follows for vehicle, 75, 200, 600, 1,800, 2,500, 5,000 ug/plate and positive control: TA98: 10, 14, 14, 24, 18, 16, 8, and 599 TA100: 166, 177, 188, 197, 198, 184, 177, and 574
Cytotoxic concentration	5,000 ug/plate
Genotoxic Effects	No positive findings.
Remarks for Results	The increase in revertant count reported in TA98 without metabolic activation was within the normal historical vehicle control range and not considered to be biologically relevant by the testing laboratory.
Conclusion Remarks	The test substance was considered to test negative in the bacterial reverse mutation assay.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Wagner V.O., Klug, M.L. [1999] Bacterial Reverse Mutation Assay. 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde; CAS Registry #31906-04-4. BioReliance, Rockville, MD. Study No. AA10BX.502.BTL, October 4, 1999. Maron, D.M., Ames, B.N. [1983] Revised methods for the Salmonella mutagenicity test. Mutat Res 38:3-32.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Chromosomal aberration (Evans, 1976)
Test Type	Clastogenic assay
System of Testing	Mammalian
GLP	Yes
Year	2000
Species/Strain	Chinese hamster ovary cell
Metabolic Activation	S9 from Aroclor 1254-induced rat liver
Doses/Concentration	4-hour without S9: vehicle, 200, 400, and 600 ug/ml 4-hour with S9: vehicle, 200, 800, and 900 ug/ml

	20-hour without S9: vehicle, 100, 200, and 400 ug/ml
Remarks for Test Conditions	A preliminary toxicity assay at concentrations up to 2,100 ug/ml was conducted to determine appropriate test concentrations. Dimethyl sulfoxide was used as the test vehicle. Chinese hamster ovary cells were treated for 4 or 20 hours in the absence of S9 or they were treated for 4 hours in the presence of S9. At 20 hours, all cells were harvested. 50% cell growth inhibition compared to vehicle control was considered substantial toxicity. Cells were seeded in flasks and incubated at 37 deg C for 16-24 hours. Duplicate cultures were exposed to lyral, positive controls (Mitomycin C and cyclophosphamide), and DMSO vehicle. In cultures without S9, cells were exposed to the test substance for 4 hours after which the treatment medium was removed, the cells were washed with CMF-PBS, and then re-incubated in complete medium. Cultures without S9 also were exposed continuously to the test substance for 20 hours. Two hours prior to harvest (at 20 hours after treatment initialization), 0.1 ug Colcemid/ml was added to the flasks. Cultures incubated in the presence of S9 were treated exactly the same as those exposed without S9 for 4 hours. Cells were collected and stored overnight in fixative at 2-8 deg C. Slides were prepared using Giemsa staining and metaphase cells with 20+/-2 centromeres were examined under oil immersion and evaluated. If a positive result was obtained in the non-activated 4-hour group, then the non-activated 20-hour group was not evaluated for chromosome aberrations. An attempt was made to examine a minimum of 100 metaphase spreads per duplicate flask and score for chromatid-type and chromosome-type aberrations. For both S9 and non-S9 systems, a concurrent toxicity test was performed by removing an aliquot of cell suspension post cell harvest. Cells in the aliquot were counted using a Coulter counter, precipitate was noted, and cell viability was determined using trypan blue dye. Cell growth inhibition relative to DMSO vehicle were determined using cell counts and percent viability. The test substance was considered positive if the percentage of cells with aberrations showed a dose-related increase with one or more concentrations showing statistical significance (p<=0.05). The number and types of aberrations found, the percentage of structurally and numerically damaged cells (percent aberrant cells) in the total population of cells examined, and the mean aberrations per cell was calculated and reported for each group.
Results	Percent cells with aberrations (structural) **=p<=0.01: 4-hour without S9 for vehicle, 200, 400, 600 ug/ml and MMC: 0.0, 0.0, 7.0**, 0.5, and 12.0** 4-hour with S9 for vehicle, 200, 800, 900 ug/ml, and CP: 0.5, 8.5**, 11.0**, 24,0**, and 22.5** 20-hour without S9 for vehicle, 100, 200, 400 ug/ml, and MMC: 0.0, 0.5, 1.5, 3.5**, and 13.0** Percent cells with aberrations (numerical) :

	4-hour without S9 for vehicle, 200, 400, 600 ug/ml and MMC: 1.5, 0.5, 2.0, 3.5, and 3.5 4-hour with S9 for vehicle, 200, 800, 900 ug/ml, and CP: 3.5, 4.5, 4.0, 5.5, and 4.5 20-hour without S9 for vehicle, 100, 200, 400 ug/ml, and MMC: 2.0, 2.5, 1.0, 2.0, and 2.5
Cytotoxic concentration	Greater than or equal to 630 ug/ml at 4 hours without S9; 2,100 ug/ml at 4 hours with S9; 210 and 2,100 ug/ml at 20 hours without S9
Genotoxic Effects	Lyral was considered to induce structural chromosomal aberrations in the presence of S9, but not in the absence of S9. Lyral did not induce numerical chromosome aberrations in the presence or absence of S9.
Appropriate statistical evaluations?	Yes. Fisher's exact test and Cochran-Armitage test.
Remarks for Results	Since the statistically significant increase in the percentage of structurally aberrant cells at 400 ug/ml in the non-activated 4-hour group (7%) was only 1% outside of the historical solvent control range (0-6%) and in the non-activated 20-hour group (3.5%) was within the historical control range, these increases were not considered by the study authors to be biologically significant.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Gudi R. and Schadly, E.H. [2000] In Vitro Mammalian chromosome Aberration Test. 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde; CAS Registry #31906-04-4. BioReliance, Rockville, MD. Study No. AA10BX.331.BTL, May 19, 2000. Evans, H.J. [1976] Cytological methods for detecting chemical mutagens. In: Hollaender, A. (Ed.) Chemical Mutagens, Principles and Methods for their Detection. Volume 4. Plenum Press, New York.

4.2.2 *In vivo* Genotoxicity

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Micronucleus test (Heddle, 1973; Hayashi *et al*., 1994)
Test Type	Clastogenic assay

GLP	Yes
Year	2000
Species/Strain	Mouse/ICR
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	Corn oil vehicle, 225, 450, and 900 mg/kg bw
Exposure Period	Single dose
Remarks for Test Conditions	A micronucleus test was conducted according to established procedures using groups of male and female ICR mice administered three dose levels of test material in corn oil by a single intraperitoneal injection (5 mice/sex/dose). Vehicle control mice were dosed with corn oil and the positive control was cyclophosphamide (2.5 mg/ml). Mice were sacrificed at 24 or 48 hours, and bone marrow cells collected from the femur. Glass slides were prepared using the bone marrow suspension. The number of micronucleated normochromatic erythrocytes were scored for the presence of micronuclei and the proportion of polychromatic erythrocytes to total erythrocytes was recorded. A response was considered positive if a dose-responsive increase in micronucleated polychromatic erythrocytes was observed and one or more of the doses were statistically evaluated relative to the vehicle control.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	None
Appropriate statistical evaluations	Yes. Kastenbaum-Bowman
Conclusion Remarks	Lyral did not induce micronucleated polychromatic erythrocytes in mouse bone marrow.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Cocchiara, J. A.M.Api and D.Jacobson-Kram. (2001) In vitro and in vivo evaluation of the genotoxic potential of three aldehydes used as fragrance ingredients. *The Toxicologist*, 60(1), 101-102.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data is for structurally related substance hydroxycitronellol

Method/guideline	Sex linked recessive lethal mutation assay (Wuergler *et al.,* 1977)
Test Type	Lethal mutation test
GLP	No
Year	1982
Species/Strain	*Drosophila melanogaster*
Sex	Not reported
Route of Administration	Oral-Diet
Doses/Concentration	10 mM
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Genotoxic effects	None
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for Results	Number (%) of sex-linked recessive lethals/chromosomes tested for Brood I, II, and III, respectively: 3/1,227; 1/1,208; and 0/1,211.
Conclusion Remarks	Hydroxycitronellol did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Wild D., King M.-T., Gocke E. and Eckhardt K. (1983). Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Fd Chem Toxicol 21(6):707-719. Kastenbaum M.A. and Bowman K.O. (1970). Tables for determining the statistical significance of mutation frequencies. Mutat Res 9:527. Wuergler F.E., Sobels F.H., and Vogel E. (1977). Drosophila as assay system for detecting genetic changes. In Handbook of Mutagenicity Test Procedures. Kilbey, B.J., Legator, M., Nichols W. and Ramel C. (eds.) Elsevier, Amsterdam, p. 335.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Method/guideline	Micronucleus test (Heddle, 1973; Hayashi *et al*., 1994; Mavournin *et al*., 1990)

Test Type	Clastogenic assay
GLP	Yes
Year	2000
Species/Strain	Mouse/ICR
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	Corn oil vehicle, 225, 450, and 900 mg/kg bw
Exposure Period	Single dose
Remarks for Test Conditions	A preliminary pilot study and toxicity assay were conducted to determine appropriate dosages for the micronucleus assay. Groups of 5 male and 5 female mice were intraperitoneally injected with corn oil vehicle, 225, 450 or 900 mg lyral/kg bw. Ten additional mice per sex were given the high-dose and 5/sex were designated as replacement animals in the event of high mortality and 5/sex were used for bone marrow collection at 48 hours. Similarly, an additional 5 mice/sex were given corn oil vehicle and used for bone marrow collection at 48 hours. Positive control mice were administered 50 mg cyclophosphamide/kg bw. At 24 hours, and, in the case of vehicle and high-dose mice, at 48 hours, mice were killed, femurs were exposed and bone marrow was removed. Two slides per mouse were prepared and were fixed in methanol, stained with May-Gruenwald-Giemsa and permanently mounted. Two thousand polychromatic erythrocytes were scored for the presence of micronuclei using oil immersion. The number of micronucleated normochromatic erythrocytes was counted and the proportion of polychromatic erythrocytes to total erythrocytes was determined. A positive response was concluded if a dose-related increase in micronucleated polychromatic erythrocytes was reported with one or more doses showing a statistically significant increase relative to the vehicle control.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Piloerection and lethargy were noted in all mice treated with lyral. At 900 mg/kg bw, one female mouse died and was replaced with one from the designated replacements. In addition, mice of both sexes showed irregular breathing at the highest dose. PCE/Total Erythrocytes (mean) at 24 hours for corn oil vehicle, 225, 450, 900 mg/kg bw, and CP: Males: 0.544, 0.486, 0.429, 0.406, and 0.339 Females: 0.515, 0.395, 0.403, 0.415, and 0.350 PCE/Total Erythrocytes (mean) at 48 hours for corn oil vehicle, and 900 mg/kg bw: Males: 0.539 and 0.372

	Females: 0.526 and 0.385
Genotoxic effects	None
Appropriate statistical evaluations	Yes. Kastenbaum-Bowman
Conclusion Remarks	Lyral did not induce micronucleated polychromatic erythrocytes in mouse bone marrow.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Gudi R. and Krsmanovic, L. (2000) Mammalian Erythrocyte Micronucleus Test. 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde; CAS Registry #31906-04-4. BioReliance, Rockville, MD. Study No. AA10BX.123.BTL, June 30, 2000. Heddle, J.A. [1973] A rapid in vivo test for chromosomal damage. Mutat Res 18:187-190. Hayashi, M., Tice, R.R., MacGregor, J.T., Anderson, D., Blakey, D.H., Dirsch-Volders, M., Oleson, Jr., F.G., Pacchierotti, F., Romagna, F., Shimada, H., Sutou, S., Vannier, B. [1994] In vivo rodent erythrocyte micronucleus assay. Mutat Res 312:293-304. Mavournin, K.H., Blakey, D.H., Cimino, M.C., Salamone, M.F., Heddle, J.A. [1990] The in vivo micronucleus assay in mammalian bone marrow and peripheral blood. A report of the US Environmental Protection Agency Gene-Tox Program. Mutat Res 239:29-80.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data is for structurally related substance hydroxycitronellol
Method/guideline	Micronucleus test
Test Type	Clastogenic assay
GLP	No
Year	1982
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	0, 516, 860, and 1,204 mg/kg

Exposure Period	Single dose
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were given a single intraperitoneal injection of 0, 516, 860, or 1,204 mg/kg bw of hydroxycitronellol. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 516, 860, and 1,204 mg/kg bw was 2.0, 2.2, 2.2, and 2.6 respectively.
Genotoxic effects	None
NOEL (C)/ LOEL (C)	1,204 mg/kg bw
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Conclusion Remarks	Hydroxycitronellol did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Wild D. King, M.-T., Gocke, E. and Eckhardt K. (1983) Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Fd Chem Toxicol 21(6):707-719. Kastenbaum, M.A. and Bowman, K.O. (1970). Tables for determining the statistical significance of mutation frequencies. Mutat Res 9:527. Schmid, W. [1976] The micronucleus test for cytogenetic analysis. In: Hollaender, A. (ed) Chemical Mutagens, Vol. 4, p. 31. Plenum Press, NY.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data is for structurally related substance 7-hydroxycitronellal
Method/guideline	Micronucleus test
Test Type	Clastogenic assay
GLP	No
Year	1982
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal

Doses/Concentration	0, 345, 603, and 861 mg/kg
Exposure Period	Single dose
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were given a single intraperitoneal injection of 0, 345, 603, and 861 mg hydroxycitronellal/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 345, 603, and 861 mg/kg bw was 1.5, 1.5, 1.0, and 2.0, respectively.
Genotoxic effects	None
NOEL (C)/ LOEL (C)	861 mg/kg bw
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Conclusion Remarks	Hydroxycitronellal did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Wild D., King, M.-T., Gocke E. and Eckhardt K. (1983). Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Fd Chem Toxicol 21(6):707-719. Kastenbaum, M.A. and Bowman, K.O. (1970). Tables for determining the statistical significance of mutation frequencies. Mutat Res 9:527. Schmid, W. [1976] The micronucleus test for cytogenetic analysis. In: Hollaender, A. (ed) Chemical Mutagens, Vol. 4, p. 31. Plenum Press, NY.

4.3 Repeated Dose Toxicity

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Mixture of 22% 3-isomer and 76% 4-isomer
Method/guideline	Commission Directive 96/54/EC (Method B7) and OECD Guidelines for Testing of Chemicals No. 407 "Repeated Dose 28 Day Oral Toxicity Study in Rodents

GLP	Yes
Year	2006
Species/strain	Sprague-Dawley Crl:CD(SD)IGS BR strain (5/sex/group)
Sex	Male and Female
Route of Administration	Oral-Intragastric in Arachis oil BP (4ml/kg)
Doses/concentration Levels	15, 150, or 1000 mg/kg bw
Exposure Period	28 days
Frequency of Treatment	Daily
Remarks for Test Conditions	The test material was administered to three groups, each of five male and five female Sprague-Dawley Crl:CD(SD)IGS BR strain rats for up to 28 consecutive days. A control group of five males and five females was dosed with the vehicle alone (Arachis oil BP). The animals were acclimatised for 7 days. At the start of treatment the males weighed 145 to 185 grams and the females weighed 128 to 166 grams. The animals were approximately 6-8 weeks old. Animals were housed in groups of five by sex in polypropylene grid-floor cages suspended over trays lined with absorbent paper. The animals were allowed free access to food and water. A pelleted diet (Rodent 5LF2 (Certified) Diet) was used. Mains drinking water was supplied from polycarbonate bottles attached to the cage. The animals were housed in a single air-conditioned room with an air exchange rate of at least 15 air changes per hour and the low intensity lighting was controlled to give twelve hours continuous light and twelve hours darkness. The temperature and relative humidity were set to achieve target values of 21 +/- 2 C and 55 +/- 15%, respectively. Dose levels were 15, 160 and 1000 mg/kg/day at a volume of 4 ml/kg. All animals were examined for overt signs of toxicity, ill-health or behavioural changes immediately before dosing, immediately post dosing and one and five hours after dosing during the working week. Animals were observed immediately before dosing and one hour after dosing at weekends. Prior to the start of treatment and on Days 3, 10, 17 and 24, all animals were observed for signs of functional/behavioural toxicity. Functional performance tests were also performed on all animals during Week 4, together with an assessment of sensory reactivity to different stimuli. Observations were carried out from approximately two hours after dosing on each occasion. All animals were subjected to gross necropsy examination and histopathological evaluation of selected tissues was performed. Statistical analyses were performed.
NOAEL(NOEL)	150 mg/kg per day
LOAEL(LOEL)	1000 mg/kg per day
Toxic Response/effects by Dose Level	At 1000 mg/kg bw dose was mg/kg/day, clinical signs included transient increased salivation around the time of dosing from Day 3 onwards. Isolated incidents of red/brown staining around

	the mouth and scab formation (males only) were also evident between Day 13 and 25. Episodes of respiratory pattern changes and hunched posture were evident in animals of either sex treated at this dose level during the final two weeks of the study. Males treated at this dose level showed a reduction in bodyweight gain during Week 1. Females treated at this dose level showed a slight reduction in bodyweight gain during Week 1 and 4 only. Males showed a reduction in food consumption and food efficiency during Week 1 only. No adverse effect on food consumption or food efficiency was detected in females. Animals of either sex showed an increase in plasma enzymes, albumin and albumin/globulin ratio. In addition males also showed a reduction in plasma cholesterol, total protein and glucose. Animals of either sex showed an increase in absolute and relative liver weight. Males also showed an increase in absolute and relative kidney weight compared with controls. Histopathology revealed centrilobular or generalized hepatocyte enlargement, frequently with associated focal centrilobular inflammatory cell infiltrates for animals of either sex. These changes were considered treatment related. In addition, centrilobular hepatocyte necrosis was seen for males treated at this dose level. In the kidney, the proximal tubular epithelium of males was observed to be generally denser than that for control rats. At 150 mg/kg bw dose level, males showed a reduction in bodyweight gain. In females, treated with 150 mg/kg/day, alanine aminotransferase and alkaline phosphatase were increased. Males treated at this dose level showed increased albumin levels and a reduction in cholesterol. Males showed an increase in absolute and relative liver weight. Histopathology of the liver revealed hepatocyte enlargement in 3 males at this dose level. However, these changes were considered adaptive. In isolation, this was considered not to represent "serious damage" to health as defined by the criteria given in the EC labelling guide of Commission Directive 2001/59/EC. Therefore, 150 mg/kg/day may be regarded as a NOAEL for female and male rats. There were no effects at 15 mg/kg bw dose level.
Remarks for Results	The oral administration of the test material to male and female rats for 28 consecutive days at dose levels of 15, 150 and 1000 mg/kg/day in Arachis oil BP resulted in treatment related effects in animals of either sex treated with 1000 mg/kg/day and in certain end points in females and males treated with 150 mg/kg/day. The No Observed Effect Level (NOEL) was, therefore considered to be 15 mg/kg/day for female and male rats. The histopathologic changes detected at 150 mg/kg/day were confined to adaptive liver changes in three males. In isolation this was considered not to represent "serious damage" to health as defined by the criteria given in the EC labelling guide of Commission Directive 2001/59/EC. Therefore, 150 mg/kg/day may be regarded as a "No Observed Adverse Effect Level" (NOAEL) for female and male rats.
Conclusion Remarks	The NOAEL for lyral in Sprague-Dawley rats is 150 mg/kg bw per day
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	Code 1. Study performed using established guidelines/standards.
References	Dunster, J., J.McKenzie and P.Brooks (2006) 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde: Twenty-eight day repeated dose oral (gavage) toxicity study in the rat. Private Communication to RIFM. Unpublished Report.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data for structurally related substance, 4-isopropenyl-1-cyclohexencarbinol
Method/guideline	90-Day oral study
GLP	Ambiguous
Year	1996
Species/strain	Rat/Fischer F344
Sex	Male and Female
Route of Administration	Oral-Intragastric
Doses/concentration Levels	40, 120, or 400 mg/kg bw
Exposure Period	90 days
Frequency of Treatment	Daily
Remarks for Test Conditions	Groups of male and female rats (10/sex/group) were administered to 40,120, or 400 mg/kg bw of 4-isopropenyl-1-cyclohexenecarbinol by gastric intubation in soybean oil once daily for 90 days. Animals were observed daily for clinical signs and body weights were measured on weekly. Hematological examination and clinical chemistry determinations were monitored at conclusion of the study. At necropsy, organ weights were measured and histopathological evaluation was performed.
NOAEL(NOEL)	120 mg/kg per day
LOAEL(LOEL)	400 mg/kg per day
Toxic Response/effects by Dose Level	No mortalities were recorded during the study. A significant decrease in body weight was reported in the high-dose group of males. Although absolute kidney, liver and lungs weights were increased in high-dose females, there was no evidence of histopathology in any of these organs.
Remarks for Results	The authors reported that despite a significant weight loss in high-dose males, the NOEL is greater than 400 mg/kg bw per day. Based on the increased organ weights in females, the

	NOAEL was reported to be less than 400 mg/kg bw per day.
Conclusion Remarks	The NOAEL for 4-isopropenyl-1-cyclohexenecarbinol in Fischer F344 rats is 120 mg/kg bw per day
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	National Cancer Institute (1996) Clinical Development Plan: l-Perillyl alcohol. Journal of Cellular Biochemistry. 26S, 137-148.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data for structurally related substance 7- hydroxycitronellal
Method/guideline	2-year feeding study
GLP	No
Year	1967
Species/strain	Rat
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0.1 and 0.5% in the diet (approximately 50 and 250 mg/kg bw/day)
Exposure Period	2 years
Frequency of Treatment	Daily
Control Group	Basal diet
Remarks for Test Conditions	Groups of rats of both sexes were fed a diet containing hydroxycitronellal at 0.1 (10 rats/sex) or 0.5% (20 rats/sex) for a period of 2 years. At the end of the study, rats were necropsied and microscopic examinations were performed on the liver, heart, pancreas, adrenals, spleen, brain, and gross lesions.
NOAEL(NOEL)	0.5% (250 mg/kg bw/day)
Toxic Response/effects by Dose Level	No adverse effects were reported. The number of rats at the beginning of the study, after 1 year, after 1.5 years and at the end of the study were as follows: 0.1%: 20, 10, 7, and 5 0.5%: 60, 50, 48, and 31
Remarks for Results	This study was reported in German.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Bär F. and Griepentrog F. (1967) Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel für Lebensmittel. Med Emahr 8:244.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data for structurally related substance 4,4-dimethyl-3-cyclohexenecarboxaldehyde
Method/guideline	9-Day vapor inhalation toxicity study
GLP	Yes
Year	1992
Species/strain	Rat/CD
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	0, 50, 125 and 250 ppm
Exposure Period	6 hours
Frequency of Treatment	Daily for 4 consecutive days, 2 days off, then another 5 consecutive days
Control Group	Yes
Remarks for Test Conditions	Groups of 10 rats/sex were exposed to 0, 50, 125 or 250 ppm aldehyde AA vapor, 6 hours/day for 9 exposures. An additional 5 rats/sex were assigned to the control and high concentration groups for inclusion in a 4-week recovery period. The vapor was generated using a reservoir system in which compressed air was blown across the head space of liquid test substance. The test chambers were analyzed for 4,4-dimethyl-3-cyclohexenecarboxaldehyde content 4 times during the 6-hour exposure period. The chamber O2 content was 20.8%. Animals were observed daily for clinical signs, body weights were measured on days 2, 4, 7, 8, and termination, hematology and clinical chemistry determinations were conducted, and necropsies were performed. *alpha*-2 micro-globulin immunohistochemical evaluations were conducted on males from the day 12 terminations.
LOAEL(LOEL)	50 ppm
Toxic Response/effects by Dose Level	50 ppm: decreased bw gain on days 1-2 in males; increased water consumption for days 9-10 in males, increased water consumption for days 1-9 and 9-11 in females; increased serum urea nitrogen values in males; increased incidence of higher

	values for bilirubin, urobilinogen and amorphous phosphates in males on day 11 125 ppm: swollen periocular tissue; decreased bw gain on days 1-2; increased water consumption for days 9-10 in males, increased water consumption for days 1-9 and 9-11 in females; increased serum urea nitrogen values in males; increased urine osmolalities in males on day 11; increased incidence of higher values for bilirubin, urobilinogen and amorphous phosphates in males on day 11; increased relative liver weights in males; exposure related increase in renal tubular immunohistochemical staining for *alpha*-2micro-globulin in males 250 ppm: swollen periocular tissue, periocular encrustation, alopecia; decreased bw gain on days 1-2 in males, increased bw gain on days 2-4 in males, decreased bw gain on days 1-2 in females; increased water consumption for days 1-10 in males, increased water consumption for days 1-9 and 9-11 in females; corneal lesions; after the recovery period females had decreased total erythrocytes, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration values; after the recovery period females also showed increased segmented neutrophils and decreased monocytes; increased serum urea nitrogen values; increased urine osmolalities in males on day 11; increased incidence of higher values for bilirubin, urobilinogen and amorphous phosphates in males on day 11; increased incidence of bilirubin and urobilinogen in the urine of females on day 12; after recovery period females showed slightly increased protein in the urine; increased relative liver and kidney weights in males; exposure related increase in renal tubular immunohistochemical staining for *alpha*-2micro-globulin in males
Appropriate statistical evaluations?	Yes, ANOVA, t-tests, Kruskal-Wallis test, Mann-Whitney U-test, Fisher's exact test.
Conclusion Remarks	4,4-dimethyl-3-cyclohexenecarboxaldehyde appears to be a ocular and respiratory irritant at vapor concentrations of 125 ppm and higher.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Norris J.C. and Kintigh, W.J. (1994) (Crude) Aldehyde AA: Nine-day vapor inhalation toxicity study in rats. Bushy Run Research Center, Export, PA. Project ID No. 92U1012. Dated December 16, 1994.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4

Remarks for Test Substance	Data for structurally related substance 7-hydroxycitronellal
Method/guideline	Subchronic inhalation toxicity study
GLP	Ambiguous
Year	1999
Species/strain	Rat/CD
Sex	Female
Route of Administration	Inhalation
Doses/concentration Levels	Mixture:50 mg/m3 Hydroxycitronellal: 211 ug/m3
Exposure Period	13 weeks
Frequency of Treatment	4 hour/day, 5 days/week
Remarks for Test Conditions	Twelve animals per test group were subjected to a whole body inhalation exposure experiment. Aerodynamic mean diameter of particle size was 0.5 um. Animals were sacrificed 1 to 2 days following exposure. Hematological examination at week 13 involved measurement of white blood cell count, mean corpuscular volume, hemoglobin concentration, and hematocrit. Clinical chemistry examinations were performed at weeks 6 or 7 and week 13. At necropsy, gross pathological examination was performed on 24 organs and tissues including the uterus, testes and ovaries. Histopathological examination was performed on the trachea, lungs, adrenals, brain, esophagus, heart, kidneys, liver pancreas, spleen, sternum, testes, uterus and bone marrow taken from the femur. Data from all studies were subjected to a Student's t-test. The significance level was chosen to be P less than 0.05.
NOAEL(NOEL)	211 ug/m3
Toxic Response/effects by Dose Level	No toxicologically significant effects on animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters were reported and no gross pathological or histopathological findings were observed.
Appropriate statistical evaluations?	Yes. Student's t-test.
Remarks for Results	There were no adverse effects reported after female rats were exposed to an aerosol mixture (50 mg/m3) containing 211 ug/m3 of 7-hydroxycitronellal for 4 hours daily, 5 days per week for 13 weeks.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Fukayama M.Y., Easterday, O.D., Serafino, P.A., Renskers, K.J., North-Root, H., Schrankel, K.R. (1999) Subchronic

	inhalation studies of complex fragrance mixtures in rats and hamsters. Toxicol Lett 111:175-187.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Test Substance	Data for structurally related substance 7-hydroxycitronellal
Method/guideline	Subchronic inhalation toxicity study
GLP	Ambiguous
Year	1999
Species/strain	Hamster/Syrian golden
Sex	Female
Route of Administration	Inhalation
Doses/concentration Levels	Mixture: 50 mg/m3 Hydroxycitronellal: 211 ug/m3
Exposure Period	13 weeks
Frequency of Treatment	4 hour/day, 5 days/week
Remarks for Test Conditions	Twelve animals per test group were subjected to a whole body inhalation exposure experiment. Aerodynamic mean diameter of particle size was 0.5 um. Animals were sacrificed 1 to 2 days following exposure. Hematological examination at week 13 involved measurement of white blood cell count, mean corpuscular volume, hemoglobin concentration, and hematocrit. Clinical chemistry examinations were performed at weeks 6 or 7 and week 13. At necropsy, gross pathological examination was performed on 24 organs and tissues including the uterus, testes and ovaries. Histopathological examination was performed on the trachea, lungs, adrenals, brain, esophagus, heart, kidneys, liver pancreas, spleen, sternum, testes, uterus and bone marrow taken from the femur. Data from all studies were subjected to a Student's t-test. The significance level was chosen to be P less than 0.05.
NOAEL(NOEL)	211 ug/m3
Toxic Response/effects by Dose Level	No toxicologically significant effects on animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters were reported and no gross pathological or histopathological findings were observed.
Appropriate statistical evaluations?	Yes. Student's t-test.
Remarks for Results	There were no adverse effects reported after female rats were exposed to an aerosol mixture (50 mg/m3) containing 211

	ug/m3 of 7-hydroxycitronellal for 4 hours daily, 5 days per week for 13 weeks.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Fukayama, M.Y., Easterday, O.D., Serafino, P.A., Renskers, K.J., North-Root, H., Schrankel, K.R. (1999) Subchronic inhalation studies of complex fragrance mixtures in rats and hamsters. Toxicol Lett 111:175-187.

4.4 Reproductive/Developmental Toxicity

Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data for commercial mixture of cis and trans isomers: 71% trans and 28% cis; >99%
Method/Guideline	*in vivo* One Generation Reproduction Study (OECD No. 415 Guideline Study)
GLP	Yes
Year	2006
Species/Strain	Sprague Dawley Rat/Crl:CD(SD)
Sex	Females and males
Route of Administration	Oral-Gavage
Duration of Test	Premating- 10 weeks for males and 2 wweks for females Gestation 14 days (day 7 through day 20 of gestation) Throughout lactation
Doses/Concentration	0, 25, 100, or 500 mg/kg bw
Premating Exposure period for females	14 days
Control Group and Treatment	Yes, vehicle only (Arachis oil)
Frequency of Treatment	Daily
Remarks for Test Conditions	A one-generation reproduction study was conducted with HMPCC in rats (OECD 415). HMPCC in the vehicle, Arachis oil BP, was administered orally (via gavage) at dosages of 0, 25, 100 and 500 mg/kg body weight/day to 24 Sprague-Dawley

	Crl:CD® (SD) IGS BR rats per sex per group. After 10 weeks of treatment for males and two weeks of treatment for females, animals within each dose group were paired for mating. Pregnant females were allowed to give birth and maintain their offspring until Day 21 post partum at which time all surviving females and offspring were sacrificed. Females continued to be dosed during the gestation and lactation phases.
NOAEL(NOEL)	25 mg/kg bw per day (reproductive toxicity) and 100 mg/kg bw per day for maternal toxicity
Actual dose received by dose level and sex	0, 25, 100, or 500 mg/kg bw
Appropriate statistical evaluations	Yes {Dunn (1964); Dunnett (1955);Siegel (1956); Snedecor *et al* (1967a); Snedecor *et al* (1967b); Sokal *et al* (1969a);Sokal *et al* (1969b)}
Parental data and F1 as Appropriate	The No Observable Adverse Effect Level (NOAEL) for developmental and reproductive toxicity was identified as 25 mg/kg body weight/day. The NOAEL for general maternal toxicity was 100 mg/kg body weight/day. Based on conservative calculated dermal systemic exposure levels to this fragrance ingredient from use of consumer products (0.01 mg/kg body weight/day), the current safety assessment indicates a 2,500-fold safety factor between the predicted total daily consumer exposure to HMPCC and the NOAEL observed in this study.
Offspring toxicity F1 and F2	Skin sloughing was observed in the pups at the two highest dose levels, which far exceed current exposure from consumer products. The observed skin effects occurred several days after birth, and after shedding the pups appeared normal. It was not clear from the study that was conducted whether these effects were due to pre- or post-natal exposure. The OECD 415 study protocol is not designed to elucidate individual effects in the pups. As such, the results needed further clarification.
Conclusion remarks	One mechanism for the observed skin sloughing may be caused by high doses of HMPCC that produce a functional zinc deficiency in the dams resulting in the observed effects in the offspring. This phenomenon has been observed with other materials. Skin changes, particularly those observed in the HMPCC study (acanthosis and hyperkeratosis), are among the most sensitive manifestations of zinc deficiency. The high level of perinatal death in the high dose group may also be relevant to prenatal zinc deficiency. The importance of this mechanism is that it is maternally-mediated (not direct developmental toxicity) and is only produced at high dose levels when the threshold is exceeded. A developmental study has been designed to evaluate the sources of skin sloughing observed in the present study.

Data Reliabilities Qualities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. OECD guideline study.
References	Hoberman A. M. (2006) Oral (Gavage) one generation reproduction study of HMPCC in rats. Unpublished Report to RIFM.
Substance Name	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CAS No.	31906-04-4
Remarks for Substance	Data are for white spirits dry cleaning solvent containing t-butylcyclohexane that metabolizes to 4-t-butylcyclohexanol in rats (Henningsen et al. 1987).
Test Type	Oral (Gavage) Repeated-Dose Toxicity Study of HMPCC in Adult Rats,Including Neonatal Evaluation
GLP	Yes
Year	2007
Species/Strain	Rat/Crl:CD(SD)
Sex	Male/Female
Route of Administration	Oral (gavage)
Frequency of treatment	6 hours/day on days 6-15 of gestation and days 3-20 for highest dose
Doses/Concentration	0 or 500 mg/kg bw per day
Control Group and Treatment	Yes, concurrent control
Remarks for Test Conditions	Fifty female Crl:CD(SD) rats were randomly assigned to six dosage groups. Groups I-III (n = 10) comprised the main part of the study. Groups IV-V (n = 5) comprised the satellite part of the study. The dosages of 0 [Vehicle; arachis (peanut) oil] or 500 mg/kg/day HMPCC were administered orally via gavage in a dosage volume of 4 mL/kg. Group Ia was administered the vehicle and Group II was administered HMPCC once daily from DG 0 through DG 21 or 24, *i.e.,* treated throughout gestation. Group Ib was administered the vehicle and Group III was administered HMPCC once daily from DLs 1 through 21, *i.e.,* treated throughout lactation. Group IV was administered the vehicle and Group V was administered HMPCC once daily from DG 0 through 14. Dams were euthanized by CO2 asphyxiation

	on DG 15 (Groups IV and V) or DL 21 (Groups Ia, Ib, II, and III). The following parameters were evaluated: viability, clinical observations, body weights, feed consumption and necropsy observations (if applicable). Rats assigned to Groups Ia through III were evaluated for fertility parameters, adverse clinical signs observed during parturition, duration of gestation, litter sizes, pup viability at birth and maternal behavior. Blood samples were collected on DG 15 from each rat assigned to Groups IV and V for evaluation of zinc levels. On DG 15, all rats assigned to the satellite part of the study, Groups IV and V, were euthanized and the liver of each rat was excised, weighed, and a portion evaluated for metallothionein concentrations. Whole blood samples were collected from each rat assigned to Groups Ia through III on DL 2 for evaluation of zinc levels and for clinical biochemical evaluations. Dams with no surviving pups were euthanized after the last pup was found dead or missing, presumed cannibalized. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Rats that died before scheduled termination were examined for gross lesions. Pregnancy status and uterine contents were recorded Each litter was evaluated for viability at least twice daily and the pups were counted once daily. Clinical observations were recorded once daily during the preweaning period. Pup body weights were recorded daily during the preweaning period and on the day euthanasia occurred. All surviving pups in Group Ia through III were euthanized on DL 21. Pups were examined externally for gross lesions and to identify sex. Carcasses were discarded without further evaluation.
Results	Female rats dose with 500 mg/kg of HMPCC daily by gavage during gestation only or during gestation and lactation. Pups exposed to HMPCC throughout lactation exhibit skin sloughing. Pups exposed to HMPCC only through the gestation period show no significant evidence of skin sloughing.
Remarks for Results	**Rats Treated Throughout Gestation** Administration of the 500 mg/kg/day dosage of HMPCC during the entire gestation period (Group II) resulted in the deaths of two female dams on DG 23 and euthanasia of one female dam on DL 1. The deaths of the two dams on DG 23 were associated with dystocia. Euthanasia of the third dam occurred

	on DL 1, after the death of all delivered pups; the pup deaths and need for maternal euthanasia were considered associated with effects of the 500 mg/kg/day dosage of HMPCC. The only clinical and necropsy observations attributed to the 500 mg/kg/day dosage of HMPCC (Group II) occurred in one dam that died and was associated with the death (red perivaginal substance, yellow perinasal and perioral substance, a fetus present in the vagina, and fetal material present in the stomach, associated with cannibalization of a fetus). Terminal body weights were significantly increased at 500 mg/kg/day (Group II), but the averages for absolute and relative (to terminal body weight) liver weights did not significantly differ between the two dosage groups (Groups Ia and II). During gestation, mean body weight gain at 500 mg/kg/day (Group II) was 90.3% of the vehicle control group (Group Ia) value. This reduction was not statistically significant and did not significantly affect mean body weight. Feed consumption values were reduced or significantly reduced during the first two weeks of the lactation period, reflecting the smaller live litter sizes at 500 mg/kg/day (Group II), and reduced physiological needs of the dams during the lactation period. On DL 2, maternal glucose levels, blood urea nitrogen levels and alkaline phosphatase levels and the albumin to globulin ratio were significantly increased at 500 mg/kg/day (Group II), relative to the vehicle control group (Group Ia) values. Pregnancy occurred in 9 of the 10 dams in both Groups Ia and II. Two female dams in the 500 mg/kg/day dosage group (Group II) died as the result of dystocia on DG 23, as previously described. Increased incidences of stillbirths and pup deaths near parturition at 500 mg/kg/day (Group II) resulted in euthanasia of one dam after total litter loss and in significant increases in pup death on DLs 1, 2 and 3, a slight, but significant reduction in the viability index and a tendency for a reduction in the lactation index, as compared with the vehicle control group values. Live litter sizes were significantly reduced in this dosage group (Group II) throughout the lactation period. Pup weights at 500 mg/kg/day (Group II) were reduced at birth and on DLs 2 through 5. Pups that died in the 500 mg/kg/day dosage group (Group II) often did not nurse. The incidence of pups that were cold to touch also was increased in this dosage group, an observation associated with the increased mortality. All except one of the pups (40/41) in the six litters at 500 mg/kg/day (Group II) had flaking skin observed. This effect was first observed on DLs 6, 7 or 8. These transient observations disappeared, and all surviving pups appeared normal by DL 10, 12, 13 or 16. A higher than usual incidence of umbilical hernia was noted at 500 mg/kg/day (Group II) for pups treated during gestation (Group II; two pups from one litter and one pup from another litter had this observation). It is possible that this observation was unrelated to HMPCC because it also occurred in a pup from a litter of a dam that was not administered

	HMPCC until the lactation period (Group III). No increases in the incidences of umbilical hernia were observed in the previous study of HMPCC in pregnant rats. **3.3.2. Rats Treated Throughout Lactation** No maternal deaths, clinical signs or gross lesions were attributed to treatment of lactating female dams with 500 mg/kg/day of HMPCC (Group III). One female dam at 500 mg/kg/day (Group III) was found dead after the first dosage, an event considered unrelated to HMPCC. Average terminal body weights were significantly increased at 500 mg/kg/day (Group III) which appeared to be associated with the significant increase in the absolute weight of the liver although relatively few dams were evaluated. The weight of liver relative to terminal body weight was also significantly increased. During the treatment period, maternal body weight gains in Group III tended to be reduced on DLs 4 to 7 and 7 to 10, while significant increases occurred on DLs 10 to 14. Dams at 500 mg/kg/day (Group III) had a significantly greater weight loss on DLs 14 to 21 compared to the vehicle control group (Group Ib). Reflecting these probable effects of HMPCC, average maternal body weight gain for the entire lactation period was increased at 500 mg/kg/day (Group III), and average maternal body weights were significantly increased in this dosage group on DLs 13 through 21, as compared with the vehicle control group (Group Ib) values. There were no apparent affects of HMPCC on feed consumption. At 3 hours post-treatment on DL 2, cholesterol levels were significantly less at 500 mg/kg/day (Group III) than those in the corresponding vehicle control group (Group Ib). Conversely, creatinine, aspartate aminotransferase and inorganic phosphate levels were significantly increased at 500 mg/kg/day (Group III) relative to the vehicle control group values (Group Ib). Similar to rats treated during the gestation period (Group II), the albumin to globulin ratio was significantly increased at 500 mg/kg/day (Group III), relative to the vehicle control group value (Group Ib). Each of the pregnant rats delivered litters. The viability and lactation indices were significantly reduced at 500 mg/kg/day (Group III). Despite these observations, live litter sizes were slightly larger in this dosage group (Group III) than in the vehicle control group (Group Ib) throughout the lactation period. Pup body weights tended to be reduced at 500 mg/kg/day (Group III) during the lactation period; these effects of HMPCC administered during the lactation period resulted in significantly reduced pup body weight averages on DLs 10 through 21. The numbers of litters with pups with flaking and/or peeling skin were increased in the 500 mg/kg/day dosage group (Group III). The incidence of litters with peeling skin, the more severe

	observation, was significantly increased compared with the vehicle control group value (Group Ib). Peeling skin was observed in essentially all pups in every litter in the 500 mg/kg/day dosage group (Group III); two litters had pups with flaking skin observed on DL 7; these observations progressed to peeling skin on DL 8. Peeling skin was first observed on DLs 7, 8, 9 or 10 and persisted to necropsy in 112 of the 123 surviving pups. **3.3.3. Zinc Levels** The mean zinc levels in dams administered HMPCC during gestation or lactation were generally slightly higher than those for the vehicle control group dams when measured at DG 15 (Groups IV and V) or DL 2 (Groups 1a and II and Groups Ib and III). The mean zinc levels in dams administered HPMCC during gestation and measured on DG 15 were slightly higher compared to measurements taken after treatment was stopped (DL 2; Group V versus II). The mean zinc levels in dams administered HMPCC during gestation were slightly reduced compared to those in dams administered HMPCC during lactation when measured on DL 2 (Groups II versus III). In consideration of the large standard deviations in all groups, it is questionable whether these observations are of biological importance.
Conclusion remarks	This study was designed to determine if the effects observed in the offspring in the one-generation study are related to the test material and if so, whether the effect was a result of prenatal or postnatal exposure. The 500 mg/kg/day dosage was selected because it is the dosage at which effects were observed in both the dams and the offspring. On the basis of these data, 500 mg/kg/day of HMPCC [4-(4-hydroxy-4-methylpentyl)-3cyclohexene-1-carboxaldehyde] caused mortality as a result of dystocia and adverse clinical signs in the dams treated during the gestation period (Group II). Reductions in body weight gain occurred during the gestation treatment period; although not statistically significant the reduction is toxicologically important. No apparent affects of HMPCC on body weight gain were noted during the lactation period. At terminal sacrifice, the average maternal body weight was increased. Serum chemistry parameters during early lactation, specifically glucose levels, blood urea nitrogen levels and alkaline phosphatase levels and the albumin to globulin ratio were increased by 500 mg/kg/day of HMPCC (Group II). Treatment of the dams during the lactation period (Group III) resulted in increased liver weights, body weights (with fluctuating periods of body weight gain and body weight loss) and terminal weights. Cholesterol levels were lower in dams treated during the lactation period (Group III), while creatinine, aspartate aminotransferase, inorganic phosphate levels and

	albumin to globulin ratios were increased in these dams. Treatment of dams with HMPCC during gestation or lactation had biologically important effect on zinc levels. Pup growth and viability was affected by HMPCC treatment during the gestation period (Group II), in that, increased incidences of stillbirths occurred as well as pup deaths near parturition and up to DL 3. As a result, the viability index was significantly reduced, the lactation index was reduced, and live litter sizes were significantly lower than control group values (Group Ia). Transient reductions in pup weights were noted in the F1 generation as a result of maternal treatment with HMPCC during the gestation period (Group II). Clinical signs of cold to touch, often associated with pup mortality, and transient observations of flaking occurred in F1 generation pups. These effects were observed at a dose that caused reduced maternal body weight gains and maternal mortality. Observations in the F1 generation from dams treated during lactation (Group III) included significantly reduced viability and lactation indices, reductions in pup weights that were sustained until sacrifice compared to vehicle control (Group Ib), and persistent observations of skin peeling occurred in all litters. In conclusion, when pregnant rats were treated with HMPCC during the gestation period, transient clinical signs of flaking were noted in the F1 generation pups with relatively few observations of skin peeling. This effect occurred at maternally toxic doses. Conversely, treatment of the dams with HMPCC during the lactation period, resulted in skin peeling in all F1 generation pups, without resolution, and with minimal observations of flaking prior to sacrifice.
Data Reliabilities Qualities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1.
References	Lewis E. M. and Hoberman A. (2007) Oral (Gavage) Repeated-Dose Toxicity Study of HMPCC in Adult Rats, Including Neonatal Evaluation. Report No. TIF000027. Revised Draft Final Report. Unpublished Report to RIFM.